emergency departments. An ability to use a personal computer (PC) and nonproprietary software/hardware would be convenient and cost-effective. To determine interpretive concordance from a remote-site PC, 2 blinded observers re-scored 26 consecutive Tl-201 studies that had been previously interpreted in our lab. SPECT and planar (anterior and LAO-45º views) images were modem transferred to an Internet Web page. Images were displayed in standard format using an 8 bit grey scale, 1 mb video card, 800 × 600 resolution, 17″ monitor, and a Pentium 100 mHz computer. Quality was judged adequate-high for all studies. Descriptive data: 68% male, 76% known CAD, 52% prior MI, 32% prior CABG, 68% prior PTCA, 52% exercise stress. Results (all p = ns) (MVD = multivessel CAD).

	Normal	Ischemia				
		Any	MVD	LAD	RCA	LCx
Nucl Lab	7	18	11	11	13	10
Remote PC	8	17	10	12	12	10

By individual pt, concordances for any abnormality, for MVD, and vascular territory of abnormality were 83%, 81%, and 85% respectively. *Conclusion:* This study of relatively complex scans establishes the clinical feasibility of interpretation using the Internet and a generic display configuration. Further studies are indicated to determine whether additional data or different hardware may improve results.

1027 Basic Pharmacology of Receptor Blockade

Tuesday, March 18, 1997, 3:00 p.m.–5:00 p.m.
Anaheim Convention Center, Hall E
Presentation Hour: 3:00 p.m.–4:00 p.m.

1027-173 The (R)- and (S)-Enantiomers of Beta-Blockers Are Different Drugs

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In order to investigate the clinical impact of chirality in beta-blocking drugs, we performed two randomized, double-blind, cross-over studies with two groups of 12 healthy volunteers who received single oral doses of 40 mg (R)- and 40 mg (S)-propranolol, or 50 mg (R)- and 50 mg (S)-atenolol, respectively, at intervals of 1 week. Exercise was performed prior to and 4 hours after drug intake, blood samples were taken immediately before and after exercise. Compared with baseline, heart rate during exercise was reduced by (S)-propranolol (−22%, $p < 0.001$) and (S)-atenolol (−25%, $p < 0.001$) whereas the (R)-enantiomers had no effect. At rest, the mean plasma concentration of (S)-propranolol was higher (+26%, $p < 0.001$) than that of (R)-propranolol, whereas that of (S)-atenolol was lower (−3%, $p < 0.01$) than that of (R)-atenolol. Exercise caused an increase of plasma concentrations of (S)-propranolol (+25%, $p < 0.001$) and (S)-atenolol (+44%, $p < 0.001$) whereas those of the (R)-enantiomers remained unaffected.

These data demonstrate profound and clinically significant, pharmacodynamic *and* pharmacokinetic differences between the (R)- and (S)-enantiomers of propranolol as well as those of atenolol. Therefore, we suggest that the (R)- and (S)-enantiomers of beta-blocking drugs should be recognized and used as individual drugs by themselves rather than just as "the enantiomers" of racemic drugs. According to the present state of the art, the currently used racemic mixtures should no longer be regarded as the best possible remedies in beta-blocker therapy, they rather should be replaced by the optically pure (S)-enantiomers which can nowadays be provided easily and at low costs.

1027-174 Decreased Cholesteryl Esterification by β-blocker Agents in Human Oxidized Low Density Lipoprotein

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Oxidized low density lipoprotein (LDL) taken up by macrophages via the scavenger receptor may contribute to formation of intimal foam cells. We have previously reported that several β-blocker agents have variable degrees of antioxidant potency on LDL. Moreover, previous studies have shown that β-blocker agents reduce experimental atherosclerosis in primates. Thus, in this study we investigated whether β-blocker agents may prevent LDL cholesteryl esterification induced by oxygen radicals, a key event in foam cell formation. Purified human LDL were exposed to oxygen radicals generated by $CuSO_4$ (15 μM for 20 hours at 37ºC) under control conditions, or after a 30 minute pre-incubation with the β-blocker agent propranolol, metoprolol, and acebutolol (1 and 3 μM of concentration).

β-Blocker	Propranolol		Metoprolol		Acebutolol	
Dose (μM)	1	3	1	3	1	3
MDA (% reduction)	−35*	−57*	−22	−42*	−20	−43*
CE (Control oxLDL 54 ± 3)	28 ± 2*	14 ± 2*	34 ± 2	19 ± 2*	38 ± 2	22 ± 2*

Legend. MDA: malondialdehyde; CE: cholesteryl esters (nmol/mg cell protein/12 hs). * $p < 0.05$ vs relative controls.

Our data demonstrate that β-blocker agents exert a decrease on cholesteryl esterification formation. These results were achieved with concentrations of potentially clinically use. Although these drugs are known to adversely affect lipid metabolism, inhibition of both oxidative compounds and cholesteryl esterification may reduce uptake of oxidized LDL and hence foam cell formation.

1027-175 Nipradilol, a Nitric Oxide Releasing Beta-Blocking Agent, Reverses the Severity of Myocardial Injury after Ischemia-Reperfusion in Cholesterol-Fed Rabbits

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3,4-Dihydro-8-(2-hydroxy-3-isopropylamino)-propoxy-3-nitroxy-2H-1-benzopyran (nipradilol) was designed to cancel the action of beta-adrenergic blockers on vasculature by adding nitroxy residue to beta-blocker structure. We studied the effects of chronic treatment with nipradilol (10 mg/kg/day) on the size of infarct resulting from coronary occlusion (30 min) – reperfusion (48 h) in rabbits fed with/without 1% cholesterol for 10 weeks. Propranolol (50 mg/kg/day) was used as a control. Infarct size in cholesterol-fed rabbits (69.9 ± 3.8%, $n = 10$) was significantly larger than that in noncholesterol-fed rabbits (48.8 ± 5.8%, $n = 9$, $p < 0.05$). The augmentation of infarct size in cholesterol-fed rabbits was markedly reversed by nipradilol (49.2 ± 6.4%, $n = 9$, $p < 0.05$), but not by propranolol (54.9 ± 6.3%, $n = 9$, n.s.). In noncholesterol-fed rabbits, neither nipradilol nor propranolol affected the infarct size (52.5 ± 4.8% and 61.9 ± 7.2%, respectively, n.s.). There were no significant differences in the area at risk and in hemodynamic data during the course of experiment among all groups. Acetylcholine (10^{-5} M)-induced relaxation of aorta was markedly impaired in cholesterol-fed rabbits (57 ± 5 vs. 95 ± 4%, $p < 0.05$), which was completely reversed by nipradilol (96 ± 5%, $p < 0.05$). We also studied whether or not nipradilol releases nitric oxide (NO) in smooth muscle cells. When cultures of rat aortic smooth muscle cells were treated with nipradilol (0.5 mM), nitrite concentration in the culture media significantly increased from 0.0 ± 0.3 to 36.0 ± 0.9 nmol/mg prot ($p < 0.05$), resulting in marked increase in cGMP content. These results demonstrate that chronic treatment with nipradilol of atherosclerotic animals could reverse the severity of myocardial injury after ischemia-reperfusion. These beneficial effects of nipradilol upon myocardial injury might be associated with its potency as a NO releasing agent.

1027-176 Antihypertensive and Vascular Effects of ET_A-Receptor Blockade in Dahl Salt-Sensitive Hypertension

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The involvement of endothelin (ET) in hypertension is still unclear. Our objective was to determine the effect of a new, orally available, selective ET_A-receptor antagonist, LU135252, on the blood pressure elevation and the changes of vascular structure in a model of salt-induced hypertension. Dahl salt-sensitive (DS) and Dahl salt-resistant rats (DR) were treated for 8 weeks with 4% NaCl alone or in combination with LU135252 (60 mg/kg/day in the chow). Placebo-treated rats served as controls (n = 6–8/group). The basilar and a small mesenteric artery (lumen diameter of 200 and 250–300 μm, respectively) were isolated and their geometry studied in vitro under perfused and pressurized conditions. Chronic salt administration increased systolic blood pressure by 37 ± 3 mmHg in DS rats, as compared to 1 ± 2 mmHg in control DS rats ($p < 0.05$; tail cuff method). This increase was in part prevented by concomitant LU135252 administration (19 ± 3 mmHg; $p < 0.05$ vs salt-treated DS rats). The media/lumen ratio of the basilar artery increased in the DS rats on 4% NaCl diet by eutrophic remodeling; vascular

hypertrophy was absent (growth index: 5 ± 4%, n.s.). In the mesenteric artery the increased media/lumen ratio was also observed, but involved hypertrophic remodeling (growth index: 32 ± 10%, $p < 0.05$). The ET_A-receptor antagonist LU135252 prevented the structural changes in both vascular beds ($p < 0.05$ vs salt-treated DS rats). The media/lumen ratio was significantly correlated with systolic blood pressure in basilar ($r = 0.53$, $p < 0.01$, linear regression) and mesenteric arteries ($r = 0.79$, $p < 0.0001$). LU135252 had no effect in the normotensive DR rats. These findings suggest that the long-term pressor effect of salt administration is mediated, in part, by the action of endogenous ET, acting on ET_A-receptors. Thus, selective ET_A-receptor antagonists may be therapeutically useful to lower arterial pressure and improve vascular remodeling of resistance arteries in salt sensitive individuals.

1027-177 Poor Regression in Hypertensive Alcoholic Rats on Lisinopril Therapy

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Hypertensive subjects who are also alcoholics are poorly managed. The mechanisms for this are unknown, but we hypothesised an interaction at the contractile-protein level. We tested this theory in the following groups; (a) SHR control, (b) SHR + alcohol, (c) SHR control + lisinopril, (d) SHR + alcohol + lisinopril. Alcohol was administered for 6 weeks and constituted 35% of total calories. Lisinopril was given in the diet at a dose of 5 mg/kg body weight. After 6 weeks the myofibrillary fractions were isolated by subcellular fractionation. The myofibrillary fraction of the heart was analysed by SDS-PAGE and produced 9 distinct contractile proteins. The results showed reduced amounts of myosin heavy chain (−20%, $P < 0.01$), myosin light chain (−24%, $P < 0.01$), and troponin (−21%, $P < 0.01$) in hypertensive alcoholic rats in comparison to control hypertensive rats. Hypertensive rats on lisinopril therapy showed reductions in left ventricle weight (−38%, $P < 0.001$) and tissue protein composition in comparison to control hypertensive rats. However, animals on concomitant alcohol and lisinopril had significantly higher wet weights (+20%, $P < 0.001$) and myofibrillar protein content (+24%, $P < 0.01$) than hypertensives on lisinopril. Individual contractile proteins were also higher but failed to attain significance. In conclusion, hypertensive alcoholic rats have impaired contractile composition. Alcoholic rats on lisinopril therapy show poor regression of contractile apparatus.

1027-178 Myocardial Tissue Concentrations of Amiodarone and Desethylamiodarone After Chronic Treatment: Correlation With Local Action Potential Duration

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To better understand the pharmacodynamic and electrophysiologic properties of amiodarone (A), we determined the relationship between chronic A treatment, myocardial tissue concentration (TC) of A and its metabolite desethylamiodarone (DEA), and the correlation between TC of A and DEA with local myocardial repolarization effects. Six hearts of rabbits loaded with A for 6 weeks (50 mg/kg/day) were isolated and Langendorff-perfused while monophasic action potential durations (MAPDs) were measured simultaneously at 10 sites of both ventricles during regular pacing at 600 msec cycle length. Each MAP recording site was marked and tissue excised for subsequent analysis of A and DEA TC using high-density liquid chromatography. A and DEA TC were widely disparate within a single heart and between different hearts (range 1.2 to 35.8 μg/g). Despite this variance, A and DEA TC consistently were highest within epicardial (11.2 ± 7.8 μg/g), lowest in midmyocardial (3.9 ± 2.3), and intermediate in endocardial tissue (4.6 ± 3.5). MAPD also varied widely within individual and all hearts, ranging from 130 to 210 msec despite constant 600 msec pacing. When the entire range of A and DEA TC from all 6 hearts was correlated with MAPD, a highly significant correlation was found between MAPD and DEA ($r = 0.83$, $p < 0.0001$) but not between MAPD and A ($r = 0.30$, $p = 0.04$).

Conclusions: 1) Six-weeks of A treatment result in widely disparate TC of both A and DEA within ventricular myocardium of a single hearts and within different hearts. 2) DEA but not A is responsible for significant increase in repolarization time. 3) MAPD distribution reflects this dispersed TC and accurately identifies the local repolarization prolonging effect of DEA. 4) The extremely heterogenous myocardial tissue uptake of A and DEA may help explain deficiencies in A treatment effectiveness.

1028 Clinical Cardiovascular Pharmacology III

Tuesday, March 18, 1997, 3:00 p.m.–5:00 p.m.
Anaheim Convention Center, Hall E
Presentation Hour: 4:00 p.m.–5:00 p.m.

1028-167 Effect of the Association of Different Progestogens to Estradiol 17β Therapy Upon Effort-Induced Myocardial Ischemia in Female Patients with Coronary Artery Disease

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Estrogens have a protective effect upon the cardiovascular system and Estradiol 17β (E) has been shown to have vasoactive and anti-ischemic properties. However, little is known on the cardiovascular effect of adding progestogens to estrogens in order to reduce the likelihood of the latter to facilitate uterine cancer. The aim of this randomized double-blind cross-over study was to evaluate the effect of adjunctive therapy with Progesterone (P, 45 mg/daily) or medroxyprogesterone (MPA, 10 mg/daily) to E upon exercise-induced myocardial ischemia in 18 postmenopausal women with CAD. Two pts were withdrawn during the MPA phase because of unstable angina. Compared to baseline E alone increased time to 1 mm ST↓ (325 ± 158 vs 257 ± 143 sec, $p < 0.01$). In 5 pts in whom the exercise test was negative after E + P the test become positive during E + MPA ($p < 0.01$). Compared to baseline E + P increased both time to 1 mm ST↓ and exercise time (416 ± 156 vs 257 ± 143 see, $p < 0.01$ and 435 ± 195 vs 365 ± 198 sec, $p < 0.05$, respectively). By contrast, no difference was found between baseline and E + MPA in either time to 1 mm ST↓ or exercise time (298 ± 146 vs 257 ± 143 sec, p = NS and 411 ± 202 vs 365 ± 198 sec, p = NS, respectively). In conclusion MPA but not natural P reverses the effect of chronic therapy with E upon exercise-induced myocardial ischemia. The progestogen to use in adjunct to E must be carefully chosen when menopausal pts with CAD are prescribed hormone replacement therapy.

1028-169 Safety, Pharmacokinetics, and Immunogenicity of Intravenous Administration of h5G1.1-scFv in Humans

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Complement activation during cardiopulmonary bypass (CPB) contributes to a systemic inflammatory response associated with excessive bleeding, and pulmonary and cardiac dysfunction. This is the first human clinical report of the safety, pharmacokinetics, and immunogenicity of a humanized single-chain monoclonal antibody, designated h5G1.1-scFv, which blocks the generation of C5a and C5b-9. The antibody is being evaluated in two Phase I studies. The initial study was designed as a single-blind, placebo-controlled, ascending-dose study of h5G1.1-scFv in healthy male volunteers. Subjects received a single dose of h5G1.1-scFv or placebo administered intravenously at one of four dose levels (0.2, 0.5, 1.0 or 2.0 mg/kg). In contrast to the very rapid clearance normally observed following injection of single chain antibodies, the h5G1.1-scFv displayed a serum half life of greater than 10 hours, presumably secondary to its very high affinity binding to the larger C5 protein in plasma. Prolonged systemic inhibition of the complement cascade was achieved in a dose dependent manner. At the highest dose, complement dependent hemolytic activity was completely inhibited for 4 hours and significant inhibition was observed for greater than 12 hours. The follow-on study was designed as a placebo-controlled, open-label, ascending dose study in CABG patients. A total of 4 doses plus placebo were tested with 3 cohorts in each dose. Safety data was assessed based on the WHO Recommendations. Assays were done to assess the extent of complement, leukocyte and platelet activation as well as fibrinolysis. Administration of h5G1.1-scFv up to single intravenous dose of 2 mg/kg is safe and well tolerated. Based on these preliminary biological effects, we propose that the use of an anti-C5 antibody will significantly reduce the impact of complement-mediated injuries sustained during CPB. Further clinical studies will be carried out to delineate the potential efficacy of an anti-C5 antibody.